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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/638,695	08/14/2000	David M. Stern	0575/62429/JPW/JML	1021

7590 09/27/2002

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EXAMINER	
TON, THAIAN N	
ART UNIT	PAPER NUMBER
1632	9

DATE MAILED: 09/27/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/638,695	STERN ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 June 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5,10 and 14-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,10 and 14-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' Amendment, filed 7/5/2002, Paper No. 8, has been entered. Claims 3-5, 7-9, 11-13 have been cancelled. Claims 1-2, 5 and 14 have been amended. Claims 1, 2, 5, 6, 10, 14-16 are pending and under current examination.

Any rejection made of record in the prior Office action, mailed 12/20/2001, Paper No. 6, and not made of record in the instant Office action, has been withdrawn in view of Applicants amendments to the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5, 6 and 10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does

not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed. Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

The specification fails to describe "Alzheimer's disease-like pathology" with particularity to indicate that Applicants had possession of the claimed invention. The specification does not provide guidance with regard to what "disease-like" encompasses. For example, it is unclear which pathologies or symptoms in an Alzheimer's disease-like pathology would overlap in other diseases. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art **as of Applicants effective filing date**. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). In the instant case, the claimed embodiment of any mutant human TAU gene lacks a written description. The specification fails to describe what Alzheimer's disease-like pathologies encompass and what pathologies are associated with it. The skilled artisan cannot what Alzheimer's disease-like pathologies encompass, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more

than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The prior rejection of claims 1, 2, 5, 6, 10, 14-16 under 35 U.S.C. 112, first paragraph, is maintained as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record advanced on pages 5-13 of the prior Office action.

Applicants traverse the rejection and state that the claims as amended, no longer recite the alleged limitation of "a transgenic non-human animal" and now recite a "transgenic mouse". Furthermore, Applicants state that the claims as amended now recite "Alzheimer's disease-like pathology" rather than the alleged limitation of "Alzheimer's disease." Applicants contend that the amended claims now obviate the prior rejection [see p. 41, 2nd paragraph].

In response, it is noted that the prior rejection is further directed to the lack of a phenotype disclosed by the claimed transgenic mice whose genome comprise a transgene encoding PDGF B-chain promoter operatively linked to a DNA sequence encoding ABAD, other than the anticipated expression of the transgene [see pp. 10-12 of the prior Office action]. Without knowing the phenotype of the claimed transgenic mouse, one of skill in the art would not know how to use the animal. Given that specific phenotypic alterations cannot be predictably achieved by merely transferring a gene of interest into an animal, and in the instant case, a mouse, specific guidance must be provided to enable the instant invention. The specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.

It is known in the art that ABAD has been implicated in the pathogenesis of Alzheimer's disease by potentiating cell stress induced by amyloid beta peptide through observation of increased 4-hydroxynoneal-lysine, malondialdehyde-lysine epitopes and the induction of DNA fragmentation (see p. 53, lines 22-29). The

specification discusses cases of severe metabolic stress, such as a murine stroke model in transgenic mice, in order to determine the consequences of overexpression of ABAD in cortical neurons (see p. 54, lines 21-34). Further, the specification teaches that these mice exhibit increased ATP levels in the cerebral cortex, decreased lactate levels in the cerebral cortex and lower beta-hydroxybutyrate levels in the cerebral cortex which has been subjected to cerebral ischemia; however, the specification does not provide a nexus between these observed results and the claimed uses of this mouse, for example, methods for evaluating the potential therapeutic effect of a compound for the treatment of Alzheimer's disease-like pathology in a human. The specification has not provided any correlation between the observed results and Alzheimer's disease-like pathology and furthermore, the transgenic non-human mouse, as claimed, is indicated to show an increase in basal APP. However, the specification does not provide data or teachings to show this elevated basal APP and therefore does not provide a correlation between the exemplified transgenic mouse and an Alzheimer's disease model. As such, the specification has not provided guidance as to how to make and use the claimed invention, as the specification only discloses the mice as Alzheimer's disease models, which would be used in evaluating therapeutic effects of an agent or compound for treatment of Alzheimer's disease (see p. 8, lines 11-24).

The specification teaches that the loss of synaptophysin immunoreactivity in presynaptic terminals is associated with the Alzheimer's brain. The specification

teaches that immunostaining analysis of the hippocampus of the doubly-transgenic Tg PD-ABAD mice with Tg hAPP mice with an antibody to synaptophysin demonstrated a reduction in the area of neuropil occupied by synaptophysin labeled presynatic terminals, and this would be consistent with evidence of neurotoxicity. Furthermore, it was found that examination of older mice showed increased staining with an antibody selective for the activated form of caspase 3, which is additionally an evidence of neurotoxicity (see pp. 47-48 and pp. 50-51). Although the specification teaches the generation of the doubly transgenic mice overexpressing three mutations of hAPP, it is not clear which of the Tg PD-ABAD/hAPP mice expressed the described reduction of synaptophysin, as such it is not clear what phenotype is observed with the described doubly-transgenic mice.

Accordingly, in view of the lack of guidance and direction provided by the specification for the use of the exemplified Tg PD-ABAD mice, the lack of guidance or teaching for methods of evaluating potential therapeutic effects of compounds for treatment of Alzheimer's disease in humans using any transgenic non-human mouse, the lack of guidance or teaching provided by the specification for a correlation between the observed levels of the increased ATP levels in the cerebral cortex, decreased lactate levels in the cerebral cortex and lower beta-hydroxybutyrate levels in the cerebral cortex which has been subjected to cerebral ischemia, it would have required undue experimentation for one skilled in the art to make and use the claimed transgenic non-human mice.

The prior rejection of claims 11-13 under 35 U.S.C. 112, first paragraph is rendered moot in view of Applicants' cancellation of the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The prior rejection of claims 1, 5 and 14 is withdrawn in view of Applicants' amendment to the claims.

The prior rejections of claim 9, 11 and 12 are rendered moot in view of Applicants' cancellation of the claims.

The prior rejection of

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The prior rejection of claims 1, 14, and 16 under 35 U.S.C. 103(a) is maintained as being unpatentable over Moechars *et al.* (JBC, Vol. 274, March 1999,

pp. 6483-6492) when taken with He *et al.* (**JCB**, Vol. 273, April 1998, pp. 10741-10746) for reasons of record advanced on pages 19-20 of the prior Office action.

Moechars *et al.* teach the generation of transgenic mice that overexpress different mutations of amyloid precursor protein (APP) in their brains (see *Abstract*). Moechars *et al.* teach that these mice demonstrated increased A□ levels which correlated with the formation of amyloid plaques in the brains of old APP/London transgenic mice, and after analysis of the plaques, it was found that they displayed many aspects typically observed in the brain of Alzheimer's disease patients. Moechars *et al.* teach that these mice would be good models to study Alzheimer's disease (see p. 6483, col. 2, 2nd paragraph). The transgenic mice were generated using cDNA coding for various APP forms (both wild-type and mutant), where the cloned and linearized minigenes were microinjected into prenuclear embryos, see p. 6483, 2nd column. Moechars *et al.* teach that the transgene was driven by the mouse thy-1 promoter (a nervous-tissue specific promoter) (see p. 6484, 2nd column, *Results*). Moechars *et al.* differ from the claimed invention in that they do not use a targeting construct containing human ABAD. However, prior to the time of filing, He *et al.* teach the cloning and characterization of ABAD (also known ERAB). In particular, He *et al.* teach the sequences of ABAD (see Figure 2) and discuss its role in mediating neurotoxicity in Alzheimer's disease (see *Abstract*).

Applicants argue that it would not have been obvious for one of skill in the art to combine the mouse thy-1 promoter as taught by Moechars *et al.* with the

ABAD sequences of He *et al.* because the prior art references neither teach nor suggest the transgenic mouse of the present invention exhibiting at least one phenotype from the group consisting of overexpression of ABAD, elevated levels of basal ATP; protection from metabolic or ischemic stress. Therefore, Applicants argue that the prior art references do not provide a suggestion or motivation to modify the reference teachings to produce the claimed invention [see p. 52, 2nd paragraph].

In response, it is reiterated that absent any phenotypic requirements of the claimed transgenic mouse, the combination of the cited prior art is sufficient to make obvious the claimed invention. The mere overexpression of ABAD does not constitute a phenotypic requirement, as it is well-known in the art that the introduction of a targeting construct, and in the instant case one encoding ABAD, into the genome of a mouse would produce a transgenic mouse that be anticipated to overexpress the transgene of interest, in the instant case, ABAD. As such, it is maintained that the combination of Moechars *et al.* and He *et al.* is sufficient to make obvious the claimed invention.

Accordingly, in view of the teachings of He *et al.*, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to generate transgenic mice with transgenes under the control of the thy-1 promoter as described by Moechars *et al.* with a transgene encoding ABAD, with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently

motivated to make such a modification, as asserted by He *et al.*, that because ABAD mediates neurotoxicity in Alzheimer's disease, there would be a need to examine its function in the pathogenesis of the disease.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear and convincing evidence to the contrary.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to Patsy Zimmerman, Patent Analyst, at (703) 305-2758. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703)872-9306.

Deborah Crouch

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